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TREMBLES (OR MILK SICKNESS) [1]

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Trembles and milk sickness are names both of which are used to designate a disease attacking animals and persons. The disease is caused by certain poisonous plants. White snakeroot, *Eupatorium urticaefolium* Reichard, and jimmyweed or rayless goldenrod, *Aplopappus heterophyllus* (A. Gray) Blake, are the principal plants involved, but a close relative, *A. fruticosus*, of the latter has been shown (*17*) [2] to be equally capable of causing the disease. Its range, however, is more limited than that of the other two plants. These plants contain a poisonous substance known as tremetol that has been proved to be the cause of the disease. Tremetol has been obtained from the plants and prepared in pure condition by laboratory methods.

HISTORICAL REVIEW

According to tradition milk sickness was recognized as a distinct disease in North Carolina as long ago as colonial times. As the Middle West was opened to settlement the disease appeared in Ohio, Indiana, and Illinois, and eventually in other States. It was confined to the backwoods and sparsely settled regions and was never prevalent in the larger towns and cities where it could come under the observation of trained physicians, so it is not strange that it was not described in print until after the beginning of the last century. Although Thomas Ashe (*2*) in 1806 refers to a disease prevalent among the settlers along the Ohio River which, from his description, appears to have been milk sickness, the first definite account was published by Daniel Drake (*11*), of Cincinnati, in 1810. Dr. Drake's report was based on information furnished him by Thomas Barbee, a Virginia physician, who, in the course of a journey through Ohio in 1809, had discovered in the Mad River district a disease that was new to him.

Dr. Drake investigated the report during the following year and confirmed the observations. He studied the disease with the purpose of discovering its cause, pathology, and treatment and published a

[1] This circular supersedes Farmers' Bulletion No. 1593—Trembles.
[2] Italic numbers in parentheses refer to Literature Cited, p. 10.

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number of papers on the subject (*12, 13*). Other accounts began to appear, but the printed information was confused and contradictory. Peter Smith (*22*), who was for years a traveling physician through the South and West, says:

> The yellow fever and the sick stomach I take to be the same disease, their difference being chiefly in external circumstances. They are both, properly speaking, the bilious fever.

At first the connection between the human and animal diseases was unrecognized, but it gradually became known that during the late summer and fall when "sick stomach" or "puking fever" was prevalent among the settlers there was also present the condition called "trembles" in livestock. It was observed that suckling calves sometimes sickened and died with trembles and that the dam also became sick with the same condition at the same time or soon after. An anonymous article in a Cincinnati newspaper, Liberty Hall (*1*), in 1811 describes the case of Alex. Telford and family in which the milk of four cows was suspected of conveying the disease. It soon became the current belief that the two diseases had a common cause and that the milk carried the disease from the cows to persons.

It was concluded that cows might eat some noxious substance which would pass into their milk and render this secretion poisonous to human beings. The idea spread, and soon the name "milk sickness" or "milk sick" supplanted other terms throughout the Middle West. It was thought that the flesh of animals affected with trembles would also transmit the disease, and many of the settlers abstained from meat and milk products during the autumn to avoid it.

The nature of the deleterious substance present in the poisonous milk remained obscure. Speculation as to its character was widespread and resulted in the advancement of many fantastic ideas. Poisonous dew and volatile minerals that evaporated from the earth at night, condensing on the herbage, there to await ingestion by the grazing herds; miasmata, the early conception of a germ theory; micro-organisms; various poisonous minerals, such as compounds of arsenic, copper, lead, and cobalt, as well as poisonous springs—all were advanced as explanations of the origin of the scourge. By far the most favored theory, however, and one held tenaciously from the earliest times, was that milk sickness was caused by the feeding of cows on some weed or herb that could transmit poisons to the milk.

This hypothesis was strengthened by a large number of observed facts, some of which have just been mentioned. The disease was most virulent in the late summer and early fall, particularly after a period of drought, when wholesome forage plants had been consumed and the cattle were compelled to graze on plants that they refused when other feed was plentiful. Again, cattle that were pastured in enclosed fields where weed infestation was small did not contract trembles nor did their milk cause milk sickness. It was observed that the incidence of the disease diminished as the forests were cleared and the land was brought under cultivation. Many different plants were suspected: Poison-ivy, waterhemlock, "Indian hachy", Indian-tobacco, Indian-hemp, Virginia creeper, crossvine, coralberry, marshmarigold, spurge, fools-parsley, mushrooms, and white snakeroot. It is interesting that in 1840 W. J. Barbee (*3*), of Marshall, Ill., and D. D. Owen identified the last-named plant as *Eupatorium ageratoides*, a name by which it was long classified, and made some experiments with decoc-

tions of it in which they convinced themselves of the connection of the plant with the disease. They adopted the use of sodium bicarbonate as a remedy which, in the light of our present knowledge, is a rational treatment.

Others argued that the disease was caused by parasitic fungi or by molds that grew on the plants.

Since those early days there has been a great deal of investigation of milk sickness and a large amount of literature has accumulated (*15*). The result has been that the more important facts about the disease have been determined with exactness. Its cause, course, treatment, and prevention are known, and there is no necessity for its continuance.

DISTRIBUTION AND DESCRIPTION OF THE DISEASE

Cases of trembles or milk sickness have been reported from the following States: Virginia, North Carolina, South Carolina, Georgia,

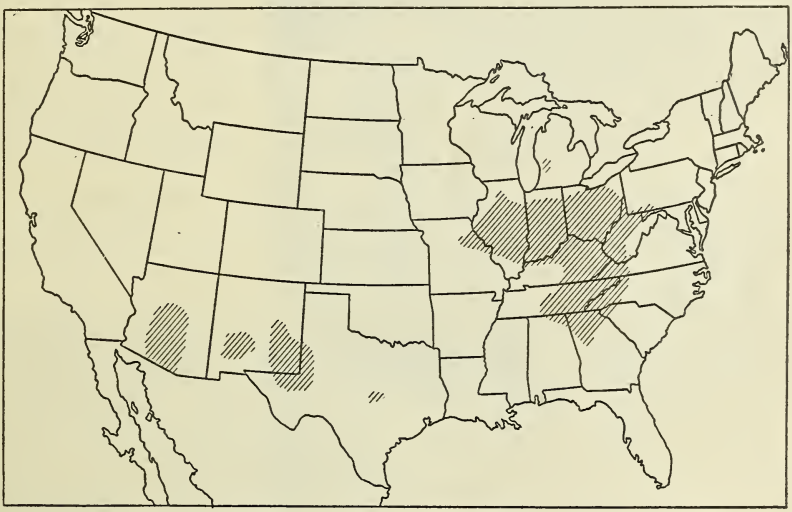

FIGURE 1.—Areas of the United States in which cases of trembles or milk sickness have been reported.

Maryland, West Virginia, Kentucky, Tennessee, Ohio, Indiana, Illinois, Missouri, Michigan, Texas, New Mexico, and Arizona (fig. 1).

The disease has been known by a number of names: Sick stomach, river sickness, tires, slows, puking fever, swamp sickness, bilious sick stomach, trembles, milk sickness, and milk sick, in the district east of the Mississippi. In the Southwest it has been called alkali disease and alkali poisoning, names that were also applied to other diseases.

The disease may be caused at any time during the life of the plants but is more common in the late summer and in early fall. It attacks many kinds of livestock. Probably no animal is immune from it. Aside from the human cases it has been observed in horses, cattle, sheep, mules, swine, chickens, rabbits, and guinea pigs. Cases have been reported also in dogs and cats.

The number of cases and the mortality cannot be stated with even reasonable accuracy. Only a few of the outbreaks are ever reported

in such a way as to be collected for medical statistics. The mortality among human beings has been estimated at about 25 percent. Wolf, Curtis, and Kaupp (*26*) collected records of 320 human cases of which 77 died. When the Middle West was being settled there was a greater prevalence of the disease on account of the lack of information about means for prevention and because so much of the pasturage was virgin forest in which white snakeroot grew abundantly. Sometimes the mortality was very high; whole villages were depopulated and many localities were abandoned by the terrified settlers. An outbreak in 1818 at Pigeon Cove, Ind., resulted in the deaths of Abraham Lincoln's mother and two of her kinsfolk, Mr. and Mrs. Sparrow (*21, v. 1, p. 30*). The early writers speak of the disease in strong terms. For example, it is "a frightful pestilence" and "a terrible malady" which "literally devastated" the country (*21*), "a very fatal disease" (*16, v. 1, p. 54*), "generally fatal to both man and beast" (*20, p. 288*). One writer states that "its terrible fatality at one period created a perfect panic in the settlers" (*14*).

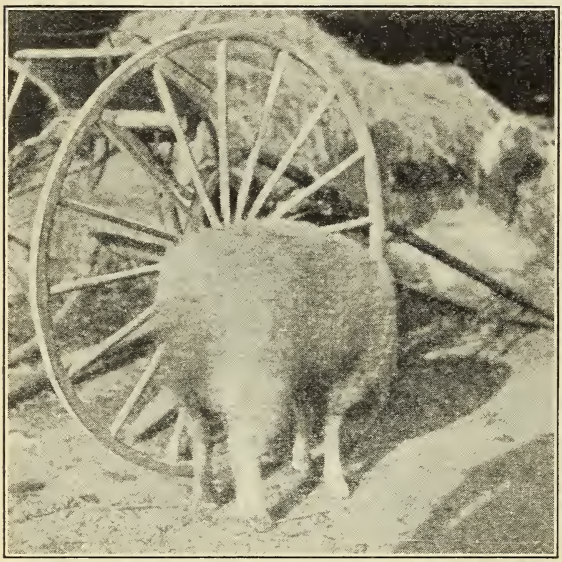

FIGURE 2.—A sheep poisoned by white snakeroot. The indistinctness of the picture of the animal was caused by its violent trembling—one of the symptoms of the disease. Note the clearness of the wheel behind the sheep.

SYMPTOMS

In human beings the first symptoms are weakness, dizziness, and loss of appetite, followed by nausea and persistent vomiting. There is pain in the region of the stomach and great thirst. The tongue is swollen and coated white, and the skin is dry. There is an odor of acetone on the breath, no peristalsis, obstinate constipation, weak pulse, slow respiration, subnormal temperature, great prostration, and frequently collapse. As the disease progresses coma develops and continues until death, which is quiet. In nonfatal cases recovery is slow. The weakness and lassitude persist for weeks, and slight exertion is very fatiguing. Relapses with fatal termination often occur during convalescence. The patient misjudges his strength and overexerts by taking a long walk or performing some laborious task about the farm, returning home to collapse and often to die within 2 or 3 days.

In animals the disease runs a course analogous to that in humans. The earliest symptom is a disinclination to exercise. The animal is depressed, does not readily rise if lying down, or moves at a slow walk when driven. With horses, cattle, and sheep, which are the animals

usually affected, this stage is followed by the characteristic "trembles" which may be the first symptom observed (fig. 2). The animal slows to a stiff-legged gait or hobble, stops with the four hoofs close together, the head hanging low and the back arched (fig. 3). The muscles of the shoulders, hips, and muzzle begin to twitch, and then a violent trembling develops during which the whole body is forcibly shaken in a longitudinal direction. In a few minutes the animal collapses (fig. 4). There is usually a strong odor of acetone on the breath and in the urine. The appetite is diminished, the temperature normal or slightly elevated, the pulse slow and weak, and the respiration during and after the spells of trembling very rapid. Constipation is generally present.

FIGURE 3.—A cow seriously affected by trembles, caused by jimmyweed; the calf in the foreground was made sick by the cow's milk.

The excretion of acetone through the lungs gives rise to a peculiar odor on the breath of milk-sickness patients. This was one of the constant symptoms mentioned by writers on the disease from the time of Drake onward. The odor was described in different ways but is so characteristic that many physicians considered it a typical symptom. Often it pervaded the house so that the physician on entering could diagnose the disease before seeing the patient. The cause of the odor is a ketosis, a condition of faulty metabolism due to the disease, a secondary manifestation of chronic tremetol poisoning. It was recognized by W. E. Walsh (*23*, *24*), of Morris, Ill., and the presence of acetone in the urine of the patients was demonstrated by R. T. Woodyatt, of the University of Chicago (*15*). The presence of acetone in the blood and urine of animals poisoned by white snakeroot or by jimmyweed has also been demonstrated (*4*). Quantities of acetone as high as 34.25 mg per 100 cc were present in the urine. In certain very mild cases no ketosis developed and these animals recovered.

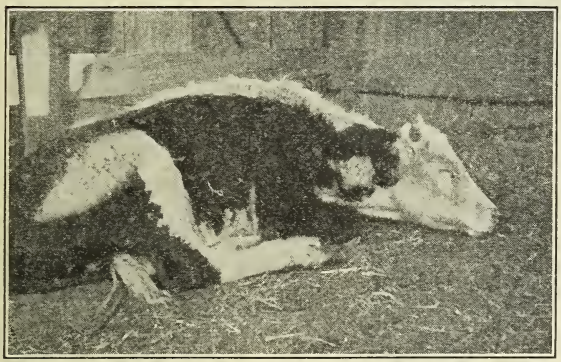

FIGURE 4.—This animal was in the last stages of the disease, which was caused by jimmyweed.

PLANTS CAUSING THE DISEASE

As already stated, the cause of milk sickness or trembles is a definite chemical compound known as tremetol (*8*). The disease is

FIGURE 5.—White snakeroot, *Eupatorium urticaefolium*.

really chronic tremetol poisoning. This substance is a viscous levorotatory oil with a pleasant aromatic odor, of the composition

$C_{16}H_{22}O_3$. It is classed chemically with the higher alcohols. Tremetol is insoluble in water, acids, and alkalies and soluble in the common organic solvents, alcohol, chloroform, ether, etc. The pure substance has produced trembles experimentally in sheep (*7*).

Tremetol has been found in three plants (*5*, *9*), all of which are known to produce trembles in animals. These are (1) white snakeroot, (2) jimmyweed, and (3) the close relative of the latter, *Aplopappus fruticosus*.

WHITE SNAKEROOT

White snakeroot, *Eupatorium urticaefolium* Reichard, also called *E. ageratoides* L. in older works, is an erect perennial herb of the composite family (fig. 5). The leaves are opposite, 3 to 5 inches long, broadly ovate, pointed, sharply toothed, thin, with long petioles. The small heads, each containing from 10 to 30 tiny white tubular flowers, are arranged in terminal compound corymbs and appear in late summer and early fall. The plant grows from 1 to 4 feet in height. It occurs widely throughout the eastern part of the United States and as far west as Minnesota, Nebraska, Oklahoma, and Texas. It is most commonly found in open woods in moist locations but often grows in the open in cleared ground.

It is commonly known as white snakeroot throughout the Middle West, but has also been termed richweed (*6*), white sanicle, Indian sanicle, deerwort, boneset, poolwort, poolroot, squawweed, whitetop, stevia, and snow thoroughwort.

FIGURE 6.—Jimmyweed, *Aplopappus heterophyllus*.

JIMMYWEED OR RAYLESS GOLDENROD

Jimmyweed, *Aplopappus heterophyllus* (Gray) Blake, also called *Isocoma wrightii* and *Bigelovia rusbyi*, is a stout, erect, tufted perennial herb (fig. 6) belonging to the composite family. The plant is usually from 1 to 2 feet tall but may reach 4 feet under favorable conditions. The alternate leaves are from ¾ to 2½ inches long by ⅛ to ¼ inch wide. The numerous small yellow heads are closely clustered at the top of the stem and branches, and each contains from 7 to 15 tubular disk flowers. It grows from southern Colorado to western Texas, New Mexico, and Arizona, and extends southward into Mexico.

APLOPAPPUS FRUTICOSUS

Aplopappus fruticosus,[3] a species having no well-known common name, is similar to *A. heterophyllus*. The principal distinction is that in *A. fruticosus* the leaves are divided into 2 to 6 pairs of very narrow

[3] This description has been furnished by S. F. Blake, senior botanist, Bureau of Plant Industry.

lobes, whereas in *A. heterophyllus* the leaves are entire or merely toothed. *A. fruticosus* occurs in Arizona, Texas, and Mexico.

TRANSMISSION THROUGH MILK

Independent observations by a number of investigators have established the fact that milk sickness or trembles can be transmitted through the milk of cows or other lactating animals that have received tremetol internally either as such or by feeding on plants that contain it. Suckling calves and lambs have become sick when the dam has eaten white snakeroot or jimmyweed (rayless goldenrod) (*19*), and the symptoms exhibited by the suckling animals have not differed essentially from those shown by adult animals with trembles (fig. 7). Cream and butter from the milk have also been incriminated as conveyors of the poison. Since butter may be stored for several months before use it is possible that outbreaks of milk sickness due to poisoned butter may occur during the winter months at a time when the plants which produced the poison have been killed back by frost.

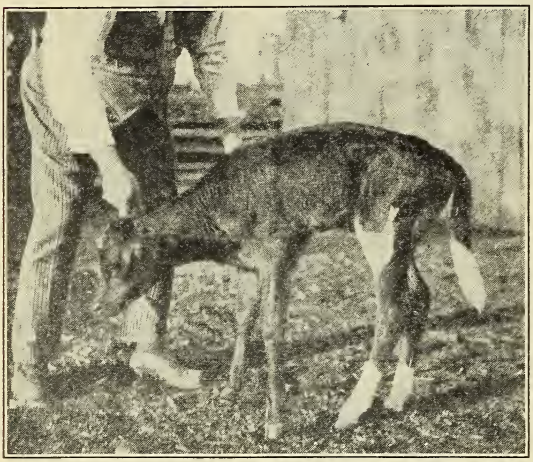

FIGURE 7.—This calf was poisoned by the milk of its mother; the cow was poisoned by white snakeroot.

Milk capable of causing the disease may be secreted by an apparently healthy cow. There are several cases recorded by physicians in which persons who drank the milk became sick and some of them died before the cows showed any symptoms of trembles. R. G. Wilkinson (*25*), of Greeneville, S.C., reports two series of cases in which the cows showed no symptoms until from 1 to 21 days after the patients became ill. M. B. Culpepper (*10*), of Carlsbad, N.Mex., records an outbreak of 6 cases in 1 family in which the cow did not sicken at all although her suckling calf died of trembles.

Outbreaks of milk sickness have usually occurred on isolated farms where the family has been drinking milk from one, or at most, a few cows. The disease has never been recorded as due to milk from creameries and is unknown in the cities and larger towns. Unlike a micro-organism, tremetol cannot propagate itself in milk and there appears to be little danger from mixed milk supplies for large communities from this source.

MEAT FROM ANIMALS DEAD FROM TREMBLES

There have been many field observations that the flesh of animals which died from trembles is capable of transmitting the disease. However, it has been impossible to confirm these reports by labora-

tory investigations. Careful feeding of such flesh to cats and dogs by Jordan and Harris (*15*), Wolf, Curtis, and Kaupp (*26*), Marsh and Clawson (*18*), and the writer has been without effect. Considered from a point of view of dosage, it is unlikely that enough tremetol could be stored in the flesh to furnish a toxic dose even when such flesh is eaten for a reasonable period.

Although tremetol is a cumulative poison, indications are that the body is able to metabolize a certain quantity of it and to convert it into harmless products. Consequently there is a certain minimum dose that must be taken each day for poisoning to result. It is unlikely that enough tremetol could be obtained from contaminated meat to supply this minimum dose.

Since cows can secrete the poison in their milk the above considerations furnish an explanation why lactating cows are unaffected when steers and dry cows in the same herd and on the same pasturage are affected by trembles.

REMEDIES

The most important procedure in treating a case of milk sickness is to remove the cause. All milk and butter should be obtained from reliable sources. Since milk-sickness patients cannot retain solid food the practice is to put them on a milk diet. If the nature of the illness is not recognized the milk served may be from the same source as that which caused the illness, and the unfortunate patient is further poisoned by the measures taken to relieve him. Immediate change of milk and butter supplies is imperative.

Medical treatment of milk sickness consists of supportive measures, combating the ketosis, and relieving the constipation. The use of enemas of glucose and sodium bicarbonate is a recognized procedure. Complete rest is necessary and during convalescence no extensive exertion should be allowed. Relapses are common and the mortality is high.

Remedies for trembles in animals consist in rest and general supportive treatment. If ketosis has not become marked the prognosis is good. A drench of sodium bicarbonate 3 or 4 times a day and a large dose of Epsom salt are recommended. Feedings of oats and a liberal supply of drinking water are of benefit.

PREVENTION

Milk sickness or trembles may be completely prevented by keeping livestock away from patches of white snakeroot in the East and jimmyweed and *Aplopappus fruticosus* in the Southwest. White snakeroot may be pulled up before seeding and piled out of reach of animals. In this way pastures may be cleared and all danger removed. Since the seeds may remain viable for some years the pastures should be inspected each year and all seedlings destroyed. Where eradication is not practicable the patches of weed should be fenced off and the livestock kept out. Jimmyweed may be dug out of pastures. The plant will be killed if it is cut off about 3 inches below the surface. This work should be done before the plant goes to seed; otherwise the dug plants should be burned to prevent reseeding. Both are perennial plants and mowing will not kill them.

SUMMARY

Milk sickness or trembles is a disease that attacks persons and lower animals alike. It is due to a poisonous substance, tremetol, present in certain poisonous plants.

In the eastern portion of this country white snakeroot is the plant that carries tremetol. In the Southwest, jimmyweed and a closely related plant, *Aplopappus fruticosus*, furnish the poison.

The poison is secreted in the milk of animals that have grazed on these plants and such milk is capable of causing the disease in persons and suckling animals.

The disease can be prevented by keeping livestock away from the plants either by fencing off the areas where the plants grow or, better, by destroying the plants.

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